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Review

Central Blood Pressure as an Index of Antihypertensive Control: Determinants and Potential Value

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ABSTRACT

The measurement of central blood pressure has generated interest as a tool in predicting cardiovascular events. The purpose of this article is to review the meaning and measurement of the central blood pressure and consider its potential value as an index of the antihypertensive response. Indirect estimation of central aortic pressures is obtained by the study of the radial pulse wave compared with a central pulse wave contour measured at the carotid or femoral artery level. The sum of the forward pressure wave created by ventricular contraction and of the reflected pressure wave from the peripheral arterial system produce the peak systolic blood pressure in the aorta. Measurement of the peripheral reflected-wave contribution to aortic blood pressure can be quantified as the augmentation index. Also, the increase in the rapidity of this travelling wave can be measured as the pulse wave velocity. These 2 parameters are considered to be valid indices of the peripheral arterial stiffness. Along with the calculation of systolic and diastolic aortic pressures, these measurements can give a better understanding of the actual central blood pressure to which core organs like heart, brain, and kidneys are submitted. There is tantalizing evidence for the potential value of central blood pressure as a useful index of antihypertensive action, but until clear evidence is obtained, its use should continue to be considered exploratory.

RÉSUMÉ

La mesure de la pression artérielle centrale a suscité l'intérêt comme outil de prédiction des événements cardiovasculaires. Le but de cet article est de passer en revue la signification et la mesure de la pression artérielle centrale, et d'examiner sa valeur potentielle comme indice de la réponse antihypertensive. L'estimation indirecte des pressions aortiques centrales est obtenue par l'étude de l'onde de pouls radiale qui est comparée au contour de l'onde de pouls centrale mesurée au niveau de la carotide ou de l'artère fémorale. La somme de l'onde de pression antérograde créée par la contraction ventriculaire et de l'onde de pression réfléchie provenant du système artériel périphérique produit la pression artérielle systolique maximale dans l'aorte. La mesure de la contribution de l'onde réfléchie périphérique à la pression artérielle aortique peut être quantifiée en tant qu'indice d'augmentation. Aussi, l'augmentation de la rapidité de cette onde progressive peut être mesurée en tant que vitesse de l'onde de pouls. Ces 2 paramètres sont considérés comme étant des indices valables de la résistance artérielle périphérique. Outre le calcul des pressions systoliques et diastoliques aortiques, ces mesures peuvent offrir une meilleure compréhension de la pression artérielle centrale actuelle à laquelle les organes principaux comme le cœur, le cerveau et les reins sont soumis. Il existe des données scientifiques intéressantes sur la valeur potentielle de la pression artérielle centrale comme indice utile de l'action antihypertensive, mais jusqu'à ce que des données scientifiques claires soient obtenues, son utilisation devrait encore être considérée de manière exploratoire.

Since its introduction more than a century ago, brachial artery measurement of blood pressure (BP) has been performed for the diagnosis of hypertension and follow-up of its treatment. Compelling evidence has supported the value of higher levels of brachial artery BP as a strong risk factor for heart disease and strokes[1] and have shown that its reduction using antihypertensive medication is associated with an improvement in prognosis.[2] There is growing evidence that measurement of central (aortic) BP, which is the pressure directly exerted on the brain, heart, and kidneys, is different from the BP measured in the arm, because of an amplification effect that increases the central BP. Hypertension is characterized by a reduction in the calibre and number of small peripheral arteries with an increase in mean arterial pressure, which is a product of cardiac output and peripheral vascular resistance.[3] These peripheral arteries are muscular, with a high proportion of collagen fibres and therefore are less distensible. In comparison, aortic and carotid arteries are predominantly made of elastin fibres. The arterial wall of these large arteries will permit filling during systole by distension and will push blood forward in a steady flow during diastole as the artery recoils. Therefore, arterial stiffness is lowest in the elastic ascending and thoracic aorta and highest in distal arteries, such as the tibial artery. Progressive loss of elasticity is encountered with

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age and hypertension and is responsible for the increase in pulse pressure (PP) in peripheral arteries.[3] The pressure wave generated by the left ventricle travels down the arterial tree and then is reflected back centrally at the arterial-arteriolar junction. Consequently, the total pressure waveform in the aorta becomes the sum of the forward travelling waveform generated by the left ventricle and the backward reflected wave from the peripheral muscular and stiffer arteries. The backward (reflected) wave causes an increase in the central peak systolic BP, generating an increased PP. This increase in total aortic PP is called the augmentation pressure (Fig. 1) and is expressed as a percentage of the total pressure by the augmentation index (AIx). Arterial stiffness of limb vessels rapidly increases with distance from the heart, leading to a narrower wave with greater systolic BP. As a result, brachial systolic BP and PP are greater than central pressures in young individuals, whereas diastolic BP is constant.[4] Hypertension, high lipid levels, and smoking all lead to increase of the central BP.[5] With aging, there is a disappearance of the PP gradient along the arterial tree, leading to greater central BP because of a more pronounced stiffening of the central rather than peripheral arteries.[4]

Measurement of Central BP and Prognostic Value

Central pressures are derived from noninvasive techniques of measurement of radial or carotid pulses, and a validated generalized transfer function is used to estimate central pressures from the peripheral signal.[6] These involve applanation tonometry, in which transcutaneous pressure transducers at the end of a probe obtain pressure waveforms that are almost identical to those obtained using intra-arterial measurement.[7] This technique is suitable for radial, carotid, or femoral arteries. The carotid waveform is then used as a surrogate for that of the aorta. Another method is a mathematical description of the charge from the input to output signals to derive an aortic waveform from measurements obtained at the radial artery. Computerized programs then adjust for heart rate, height, and age. Hence, central systolic BP, diastolic BP, and PP are obtained and indices of arterial stiffness such as AIx and pulse wave velocity (PWV) are estimated.[8] The general transfer functions of applanation tonometry have a range of error, but it is less than for standard brachial cuff pressure with a sphygmomanometer or an oscillometric device.[9] Intrinsic variations in the measurements provided by different instruments are possible and can be operator-dependent.

The measurement of the AIx, which is a quantification of the arterial wave reflection on total BP, can vary with changes in heart rate, cardiac contractility, and age. PWV is the measurement of aortic pulse velocity; it is assessed by measuring the distance between 2 arteries (usually the carotid and femoral arteries) and dividing by the transit time. Greater arterial stiffness, which means less compliant arteries, will result in quicker wave travel to and from the periphery. PWV has emerged as a better marker of arterial stiffness, because of its relative ease of measurement and reliability, although some variability has been encountered in different types of populations, with age and different BP levels. It is not influenced by smoking, dyslipidemia, or sex, but to some extent by heart rate and diabetes.[10] Mitchell and colleagues,[11] in a prospective study of 2232 participants in the Framingham Heart Study after a mean follow-up of 7.8 years, concluded that the best individual predictor of a first major cardiovascular (CV) event by a pulsatile hemodynamic measure is the PWV (Fig. 2). Vlachopoulos et al. conducted a systematic review of 15,877 subjects and concluded that aortic PWV is a strong predictor of future CV events and all-cause mortality and has a predictive value independent of classic CV risk factors and other potential confounders.[12] For total CV events and CV mortality, the relative risk of a high PWV was greater in high-risk populations compared with low-risk populations. These findings suggest that measurement of arterial stiffness can capture CV risk from a genetic background and cumulative damage from CV risk factors on the arterial wall. Recently, the Reference Values for Arterial Stiffness Collaboration group in Europe has published reference values for the PWV.[13] Although normal PWV values might overlap between younger and older individuals and many CV risk factors are not all quantifiable (stress, positive family history, and others), the mean normal value for individuals aged younger than 30 years is 6.2 m/s and for age 70 years and older is 10.9 m/s.[13]

Central BP might be a better predictor of target organ damage than standard brachial BP. For example, it correlates

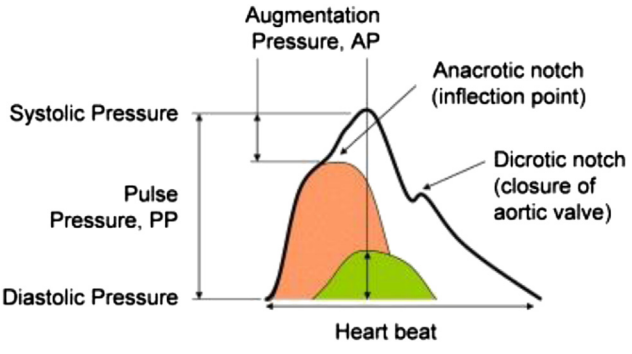

Figure 1. The augmentation index is a ratio calculated from the blood pressure waveform (augmentation index = Δ P/pulse pressure). It is a measure of the enhancement (augmentation) of central aortic pressure by a reflected pulse wave (shown in **green** in the graph). P, pressure. Reproduced with permission from USCOM.

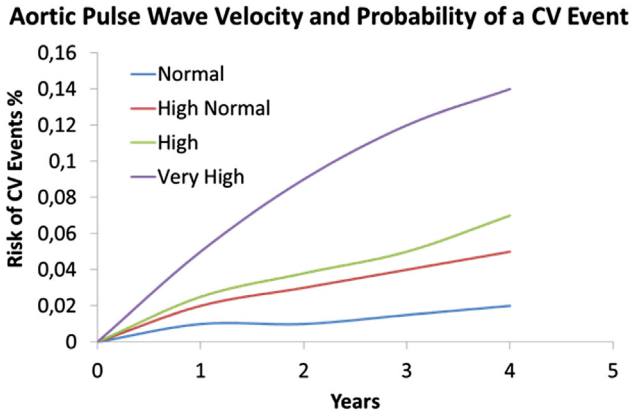

Figure 2. PWV and risk of a major CV event. The greater the PWV, the greater is the risk of a major CV event over time. CV, cardiovascular; PWV, pulse wave velocity. Data from Mitchell et al.[11]

better with carotid internal diameter and intima-media thickness than brachial BP measurements.[14] The systolic augmentation of central PP is associated with an increase in left ventricular mass index independent of age and mean BP,[15] and carotid systolic BP is an independent determinant of left ventricular wall thickness.[16] Central pressure correlates more closely with vascular hypertrophy and the extent of atherosclerosis,[14] and with CV risk in apparently healthy patients with atherosclerotic disease.[11] Increased central pressure is associated with age-related macular degeneration[17] and progression of renal disease.[18] In the Strong Heart study, a population-based study of 3520 participants, central PP was more strongly related to carotid artery vascular mass, intima-media thickness, and carotid atherosclerotic plaque score than was brachial PP.[19]

In 2002, Safar and colleagues published the first clinical evidence of the prognostic value of the measure of aortic BP.[20] In patients with end-stage renal disease, central PP measured at the carotid artery was a found to be a significant predictor of all-cause mortality and CV mortality, and brachial PP had no predictive value for mortality.[20] In the Strong Heart study, 2403 participants free of CV events at baseline with a mean follow-up of 4.8 years, the central PP predicted CV events (myocardial infarction, coronary disease, heart failure, cardiac death, and stroke) more strongly than brachial PP.[19] In patients aged 65 years and older, including normotensive and untreated hypertensive individuals followed over 8 years, greater carotid PP at baseline, but not brachial PP, predicted CV events and mortality.[21] Kaess et al. prospectively investigated the longitudinal and temporal relationships of vascular hemodynamics in participants of the Framingham Offspring cohort and found that higher aortic stiffness, forward wave amplitude, and AIx were associated with a greater risk of incident hypertension.[22] Finally, Cheng et al. have recently proposed that a diagnostic central BP number should be $\geq$ 130/90 mm Hg.[23]

Implications for Therapy

There is evidence that some antihypertensive agents might provide target organ protection beyond their effect to decrease brachial BP. Large multicentre trials comparing 2 active treatments including the Second **A**ustralian **N**ational **B**lood **P**ressure (ANBP2) study,[24] **L**osartan **I**ntervention **f**or **E**nd Point Reduction in Hypertension (LIFE),[25] **A**nglo-**S**candinavian **C**ardiac **O**utcomes **T**rial (ASCOT),[26] and **A**voiding **C**ardiovascular Events Through **Com**bination Therapy in **P**atients **Li**ving With **S**ystolic **H**ypertension (ACCOMPLISH)[27] have shown clinical benefits of BP-reducing strategies including a calcium channel blocker or a renin-angiotensin blocker (an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker) that were superior to treatments based on a β-blocker (BB) or on a thiazide diuretic for approximately the same level of peripheral (brachial) BP. This added protection that goes beyond brachial BP control could be explained by a neutral metabolic effect of some antihypertensive agents, better tolerability, and thus improved adherence. But a superior vascular protective effect on target organs or on intermediate end points such as arterial stiffness or central BP could be also related to a reduced CV morbidity or mortality. Effects on central pressures might not be evident according to pressure measurements of a peripheral (brachial) artery, because the reflected wave is added to a different part of the central waveform (ie, AIx). This might be one explanation as to why drugs that provide similar reduction in peripheral pressures have a different effect on CV outcome.

The largest randomized controlled trial conducted to test the hypothesis of clinical benefit of decreased central pressures was the **C**onduit **A**rtery **F**unction **E**valuation (CAFE) study, a substudy of the ASCOT study.[26] Radial artery applanation tonometry and pulse wave analysis were used to derive central aortic pressures and hemodynamic indices in 2199 patients from the ASCOT study.[28] Despite similar brachial systolic BPs between treatment groups (Δ 0.7 mm Hg; $P = 0.2$), there were much larger reductions using the amlodipine-based regimen in the central aortic systolic BP (Δ 4.3 mm Hg; $P < 0.0001$) and central aortic PP (Δ 3.0 mm Hg; $P < 0.0001$) compared with the atenolol-based regimen. These greater reductions in central pressures were associated with a significantly greater reduction in CV events and development of renal impairment. The study was only hypothesis-generating in this regard, but this degree of BP difference in addition to the metabolic changes could have explained the different outcomes between the 2 treatments, which produced essentially the same brachial BP. Although central BP might be a very useful index for CV risk assessment, it has not yet been tested in a randomized controlled trial with clinical end points and treatment guided by a central BP goal or arterial stiffness markers. Recently, a randomized study[29] has shown that using central BP to guide the choice of antihypertensive therapy leads to the use of less medication compared with the control group of usual care in measuring arm BP.

Antihypertensive Drugs and Arterial Stiffness

The effects of antihypertensive drugs on arterial stiffness are complex and vary with time, the arterial territory studied, and the distending pressure in the arteries. Their effect can be direct (because of vascular smooth muscle relaxation) and indirect (because of decreased wave reflection due to dilatation of muscle arteries).[30] A summary is provided in Table 1.

Thiazide diuretics generally have no effect on PWV and arterial wave reflection.[30-32] Some BBs have a favourable effect on arterial stiffness measured according to a decrease in PWV or wave reflection, but not consistently (Table 2). Atenolol (compared with nitrendipine and fosinopril) and metoprolol (compared with lisinopril) had no effect on PWV.[33-35] When comparing atenolol and metoprolol, the peripheral BP reduction was the same, but the AIx increased with use of atenolol.[36] In contrast, bisoprolol reduced PWV in only some

Table 1. Effects of hypertension medications on wave reflection and PWV

Antihypertensive class	Wave reflection (AIx)	PWV
Diuretics	NC	NC
Calcium channel blockers (dihydropyridines)	Improvement	Improvement
Angiotensin-converting enzyme inhibitors	Improvement	Improvement
Angiotensin receptor antagonists	Improvement	Improvement

AIx, augmentation index; NC, no change; PWV, pulse wave velocity.

Table 2. Effects of different β-blockers on wave reflection and PWV

β-Blocker	Wave reflection (AIx)	PWV
Propranolol	NC	NC
Atenolol	NC	Improvement
Metoprolol	Possible improvement	NC
Labetalol	Improvement	Improvement
Carvedilol	Improvement	Improvement
Nebivolol	Improvement	Improvement

AIx, augmentation index; NC, no change; PWV, pulse wave velocity.

arterial areas studied and nebivolol consistently improved PWV and AIx.[37,38] Carvedilol (not approved in Canada for hypertension) improved all central BP parameters but not as well as losartan for the AIx.[39] Calcium channel blockers, specifically dihydropyridines, reduce PWV and wave reflection, but amlodipine has not been studied; data are limited for nondihydropyridines.[30] Renin-angiotensin blockers (angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists) have been studied extensively. They induce vasodilation, reverse vascular hypertrophy, and increase arterial compliance. Globally, they all reduce the PWV and the wave reflection.[30] Finally, it is unclear if other medications with vasodilatory effects (ie, clonidine, α-blockers, and hydralazine) can improve central BP components. A summary is provided in Tables 1 and 2.

β-Blockers in Hypertension

The Canadian Hypertension Education Program recommends the use of BBs as a first line therapy for hypertension in patients who have other compelling indications such as those with coronary artery disease, who have had a myocardial infarction, or heart failure.[40] For hypertensive patients without compelling indications in a primary prevention setting, BBs are considered to provide the same CV protection as other classes of antihypertensive medications in patients younger than 60 years of age.

Newer β-Blockers and Their Effect on Central BP

All BBs reduce peripheral BP by blocking the β1 receptors in the brain, heart, and kidneys, thereby decreasing catecholamine outflow from the central nervous system, the force and rate of cardiac contraction, and the release of renin. Reduced renin will decrease the release of catecholamine and aldosterone from the adrenal glands, the formation of angiotensin II, and arterial vasoconstrictive tone. With the availability of newer BBs with cardioselectivity and vasodilatory capacities, the effect on central BP might be greater. Atenolol, metoprolol, bisoprolol, and nebivolol are cardioselective and labetolol, carvedilol, and nebivolol cause direct arterial vasodilation; carvedilol does this by a α1-adrenergic blockade, labetalol through α1-adrenergic blockade and by direct β2-receptor stimulation, and nebivolol through unique nitric oxide-mediated vasodilation that is endothelium-dependent.[41]

A number of studies suggest that newer BBs decrease central BP parameters better than older BBs for similar reductions in brachial BP. Shah et al. compared carvedilol with atenolol in hypertensive individuals over 4 weeks and found that despite equal BP-lowering, carvedilol resulted in a more favourable PP amplification and AIx by increasing arterial compliance.[42] In a double-blind randomized study, Dhakam et al.[43] compared the central hemodynamic effects of nebivolol with atenolol in previously untreated patients with isolated systolic hypertension over 5 weeks. Despite similar reductions in peripheral BP, nebivolol reduced central PP to a greater extent than atenolol. Both drugs reduced aortic stiffness, but nebivolol had less effect on the aortic AIx. In a randomized double-blind study, Redón et al.[44] treated middle-aged hypertensive patients over 10 weeks with atenolol or nebivolol. Brachial arterial pressure was decreased to the same extent in both groups, but the AIx increased to a lesser extent in the nebivolol group. Mean reductions of central systolic BP were identical and central PP reduction showed a trend in favour of nebivolol. In a longer study, Kampus et al.[45] compared metoprolol with nebivolol in a randomized double-blind study in hypertensive subjects over 1 year. Heart rate, brachial BP, and mean arterial pressure reductions were identical. However, reductions in central systolic and diastolic BPs, central PP, and left ventricular wall thickness were only significant in the nebivolol group. Finally, Vitale et al.[46] compared the effects of nebivolol or irbesartan in combination with hydrochlorothiazide in patients with newly-diagnosed hypertension. A similar, statistically significant reduction was observed for brachial BP, central BP and PP, PWV, and AIx in both groups. Thus, so far, newer BBs have a more favourable influence on arterial stiffness markers and central BP, but clinical trials are needed to test the effect, if any, of this difference on CV events.

Conclusions

Arterial stiffness is now an established CV risk factor and might prove to be a better risk index for target organ damage and CV events in the hypertension population. Detection of increased vascular stiffness can predict incident hypertension in high-risk individuals and could serve as a marker of inherent atherosclerotic risk. Central BP might have better prognostic value than peripheral BP measurements because it represents core BP to which heart, brain, and kidneys are exposed. Antihypertensive medications vary in effects on central BP and vascular stiffness, with particular heterogeneity among BBs. It remains unclear whether the use of medications to improve arterial stiffness or central BP values will translate into better clinical outcomes. Randomized prospective controlled studies comparing the effects on hard CV outcomes for antihypertensive agents with different effects on central BP are needed to answer this question.

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